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New Guidelines: "Prevention and Treatment of Tuberculosis Among Patients Infected with the Human Immunodeficiency Virus"

In 1997, over 4000 cases of tuberculosis (TB) were reported in California. Yet, TB is declining and an individual clinician in one community may have few opportunities to manage a patient with TB. As a result, clinicians may not initiate appropriate treatment when TB is suspected. The difficulties in managing TB are made more monumental in the HIV-infected patient who may be on multiple other medications, particularly those needed to treat HIV infection and HIV-related disease.

To help the clinician make decisions regarding management of HIV-infected patients with TB, new guidelines entitled: " Prevention and Treatment of Tuberculosis Among Patients Infected with Human Immunodeficiency Virus: Principles of Therapy and Revised Recommendations" were released by the Centers for Disease Control and Prevention (CDC) in the October 1998 issue of Morbidity and Mortality Weekly Report. The following report summarizes the recommendations contained within these guidelines.

Early Diagnosis of TB Infection in those with HIV and Testing For HIV Infection in those with Active TB

To minimize the negative effects of TB on the course of HIV, and to prevent spread of TB to other persons in the community, early diagnosis and effective treatment of TB among HIV-infected patients are critical. This means that all patients newly identified with HIV should be promptly tested for TB infection. Conversely, all patients with newly diagnosed TB should be rapidly tested for HIV infection. When a TB patient does not have documentation of HIV testing in the previous 6 months, the guidelines recommend that this patient undergo HIV counseling and testing.

Treatment of Active TB in HIV-Infected Patients using Rifabutin in place of Rifampin

Once active TB is identified in an HIV-infected patient, administration of anti-tuberculous drugs should be directly observed by a health care worker. Most patients with HIV and TB are candidates for the concurrent administration of antituberculous and antiretroviral drugs. In the past, the interaction between rifampin and protease inhibitors led to the discontinuation of antiviral therapy during TB treatment. The current guidelines do not recommend the use of rifampin in HIV-infected patients who are on antivirals. Instead, Rifabutin, another rifamycin that is a less potent inhibitor of the hepatic enzyme system and will not lower blood levels of protease inhibitors as markedly as rifampin, can be used instead. A useful table included in the CDC guidelines details the significant interactions between rifamycins and specific antiviral drugs.

Of note, in-vitro studies and clinical trials have demonstrated that rifabutin has equivalent antituberculous activity as rifampin.[1-4] In addition, rifabutin may have more reliable absorption than rifampin and may be better tolerated in patients with rifampin-induced hepatotoxicity. The interactions of rifabutin with other drugs such as anticonvulsants, methadone, and azoles may be less marked as well. Rifabutin, is administered 150 mg or 300 mg each day, when given as an intermittent regimen with other TB drugs.

Rifapentine, another newly introduced rifamycin, is not yet recommended by these CDC guidelines given the lack of safety and efficacy data in HIV-related TB. For those patients who cannot take a rifamycin, a streptomycin-based regimen without a rifamycin may be used to treat active TB disease but needs to be given for 9 months duration. Other first line antituberculous drugs such as isoniazid (INH), ethambutol, pyrazinamide (PZA) and streptomycin can be used with nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors without substantial drug interactions. In

summary, antiretroviral drugs should be promoted in HIV-infected patients with TB since adverse drug interactions can be avoided with the use of either rifabutin or streptomycin in place of rifampin.

The Duration of Antituberculous Treatment

For the 1998 CDC guidelines, evidence was reviewed from multiple trials studying a variety of treatment durations for uncomplicated drug-susceptible pulmonary TB. The expert panel concluded that 6-month TB regimens for HIV-infected patients were associated with a clinically acceptable (<5.4%) TB relapse rate. A six-month regimen, therefore, continues to be the standard recommended duration for uncomplicated pulmonary tuberculosis for both HIV-infected and immunocompetent patients. The six-month regimen assumes that response to treatment will be monitored carefully for both groups of patients and assumes, for the HIV-infected patient, that therapy is administered in a directly observed setting. While early clinical response and time to culture conversion has been similar for those with and without HIV infection, it is uncertain at this time whether adverse outcomes may be more common in HIV-infected patients and, therefore, careful monitoring is essential.

Monitoring for Treatment Failure

The criteria for determining the ultimate length of treatment for each patient diagnosed with TB must take into account the following: a patient's adherence in taking medications, the time to culture conversion, and the clinical and radiographic improvement. Careful monitoring of patients with TB, especially those who are HIV-infected, is necessary to prevent the development of drug resistance and further transmission of tuberculosis. A paradoxical reaction during initiation of antituberculous treatment may be observed in HIV-infected patients who are also on antiretroviral treatment; this may be confused with poor treatment response. This paradoxical reaction is manifested as a temporary accentuation of clinical symptoms and signs without toxicity or microbiologic worsening. Signs may include fever, enlarging lymphadenopathy, and worsening of radiographic findings. While the pathophysiology of this transient accentuation of symptoms is unclear, this reaction has been attributed to recovery of the patient's delayed hypersensitivity response and an increase in exposure and reaction to mycobacterial antigens after therapy is initiated. These reactions occur much more frequently in HIV-infected patients (36%) in comparison to those without HIV (2%) or to HIV-infected patients who are not on antiretrovirals (7%).[5] Despite the frequency of these reactions, patients with persistent or worsening symptoms and signs of TB during therapy should always be evaluated for treatment failure given the potential consequences. Microbiologic documentation of treatment success should be always be obtained, including specimens to document smear and culture negative status, and therapy should be prolonged for patients who have a delayed clinical or bacteriologic response.

Prevention of TB Disease Among HIV-Infected Patients with TB Infection

Twelve months of INH has been the standard regimen for treatment of TB infection in HIV-infected patients. A review of currently available data from multiple studies led the panel to issue a new recommendation that 9 months of INH treatment is adequate to prevent TB in persons co-infected with HIV and *M. tuberculosis*.

In addition to a 9-month course of INH treatment, another newly recommended option for treating TB infection is an even shorter, 2-month course of daily combined therapy using PZA and rifampin (or rifabutin). At least two trials have evaluated this 2-month regimen; one trial examined prophylaxis given intermittently (twice weekly)[6] while the other trial studied daily combination treatment.[7] The former trial demonstrated equal efficacy to a 6-month INH regimen while the second unpublished trial showed efficacy comparable to 12- month INH regimen. At this time, the CDC guidelines only recommend the daily combination of PZA and rifampin for 2 months.

Table I lists the major recommendations contained within these guidelines. Providers are encouraged to examine this document carefully in detail, particularly those clinicians caring for patients with TB and HIV coinfection. The guidelines are available through CDC's World-Wide-Web server at http://www.cdc.gov or a paper copy may be obtained by calling (202) 512-1800.

TABLE I. SUMMARY OF RECOMMENDATIONS

IDENTIFYING HIV/TB COINFECTION

- Patients with newly diagnosed TB should be promptly tested for HIV infection
- Patients with newly diagnosed HIV should be promptly tested for TB infection

TREATMENT OF ACTIVE TB IN HIV INFECTED PATIENTS

- Treatment of TB in HIV infected patients should be directly observed (DOT)
- Antiretroviral therapy should be promoted in patients with TB and HIV
- Most patients with HIV related TB are candidates for concurrent administration of antituberculous and antiretroviral drugs
- Rifampin is contraindicated for HIV-infected patients on protease inhibitors
- Rifabutin is the rifamycin drug of choice if a patient is on a protease inhibitor
- A streptomycin-based regimen without a rifamycin is another option but should be given for a minimum of 6 months

LENGTH OF ANTITUBERCULOUS THERAPY AND THERAPY RESPONSE

- A 6 month antituberculous regimen should be used for treating HIV-infected patients with pansusceptible TB, assuming response to treatment is monitored and DOT is used
- Monitoring the response to treatment of HIV-infected persons is essential for ultimately determining the length of treatment of TB and should consider: adherence, time to culture conversion, and clinical response

MANAGEMENT OF PATIENTS WITH TB INFECTION AND HIV INFECTION

- 9 months of INH daily or twice weekly **OR**
- 2 months of rifampin (or rifabutin) and pyrazinamide daily

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